## REMARKS

Status of the Claims

Claims 1-7 are pending. Claims 8-22 are withdrawn from consideration. Claims 1-7 stand rejected. Claims 1 and 3-4 are amended herein. Claims 2 and 6 are canceled. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". No new matter has been added.

Claim amendments

Claims 1 and 3-4 have been amended and claims 2 and 6 incorporated into claim 1 to overcome 35 U.S.C. 102(a), 103(a) and 112, first paragraph, rejections over **Adams** *et al.*, **Horak** *et al.*, **Hartman** *et al.*, **Kasperson** *et al.* and **Lemelson** as stated *infra*. Claim 1 incorporates dependent claim 2 to define the construct as comprising an antibody or antibody fragment. Dependent claim 6 is incorporated into claim 1 to recite that the construct is administered at least once.

Additionally, claim 1 is amended to recite the limitation that the number of administrations of the construct necessary to kill the tumor increases with the size of the tumor. The specification teaches the efficacy of the method, as amended in claim 1, against such solid tumors on page 33, lines 1-13.

Claim 3 was amended to remove lead-212 as an alpha-emittor. Additionally, claim 3 was amended to correct the isotope designation of fermium which is 255. Fermium-255 is the naturally radioactive element and Applicants submit that 155 was a typographical error. The amendment to claim 4 further limits the specific activities of the constructs. No new matter is added in these amendments.

Alpha-emittors emit particles with a high linear energy transfer over a distance in the case of bismuth of no more than about 100 microns or 0.1 mm. Furthermore, administration of these isotopes via a target specific antibody will kill about 5-6 layers of cells as the isotope decays over an effective period of time based on half-life, e.g., 3-4 hours for the bismuth isotopes (Figure 2). Thus, one can reasonably expect that in a single administration of the

bismuth radionuclide a total linear distance of (5-6 x 0.1 mm) x 2 or 1.0-1.2 mm can be traveled.

Applicants respectfully point out that it is standard in the art to use the formula (L x W x W)/2 to determine tumor volume where L is the length and where the value of L is at least equal to or a greater measurement than W, the width. Solid tumors are generally not spheroidal and this formula yields an accurate volumetric result. Thus, it is standard that when one of skill in the art is referring to tumor size or tumor diameter, the value of L is indicated.

What is important in the instant invention is the value of L as opposed to the volume of the tumor. As demonstrated above, a single administration of the bismuth radionuclide is only effective for a very small solid tumor. For this reason, the instant specification teaches that another administration would remove several more layers until the tumor cells were completely killed, therefore, the number of necessary administrations of the conjugate to effect tumor kill will increase as the tumor diameter increases (specification, page 28, lines 15-28). Although the linear transfer energy in alpha-emittors varies and thus their effective ranges vary, it is obvious

that the reasoning applied to the bismuth nuclides is applicable to the use of any of the alpha-emittors identified in that a lesser or greater LET and, by extension, range would simply require more or fewer administrations of the particular alpha-emittor.

Claim objections

Claim 6 is canceled thus rendering this rejection moot.

The 35 U.S.C. §112, first paragraph rejections

Claims 1-7 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumors of 3-5 mm in diameter in size by administering an antibody specific to the tumor and radiolabeled with an alpha-emitting construct does not reasonably provide enablement for a method of killing a tumor greater than 1 mm in size by administering any construct radiolabeled with an alpha emitting isotope. Applicants respectfully traverse this rejection.

The Examiner states that **Adams** *et al.* (*Nuclear Med Biol*, vol. 27, pp. 339-346 (2000)) teach that single chain Fv and diabody have half short-lives and are not effective in selectively killing

tumors when coupled with bismuth-213. **Adams** *et al.* administered their bismuth-213/scFv construct to tumors with a mean diameter of 5-8 mm in one trial and 2-3 mm in a second trial in single doses of 100-300 μCi. Tumor growth was inhibited but not stopped.

The Examiner states that **Horak** *et al.* (*J. Nuclear Med,* 38(12), pp. 1944-50 (Dec. 1997)) teach that tumors having a volume of 15 $mm^3$ (~3 mm in diameter) can be treated with antibodies labeled with lead-212, but that large tumors with a volume of 146 $mm^3$ (~6.5 mm in diameter) could not be so treated (p. 1948, second col., second paragraph). Similarly, **Hartman** *et al.* teach that large tumors having a volume of 936 $mm^3$ (~14.4 x 11.4 mm) could not be treated with antibodies labeled with Bi-212 (p. 4367, first col., first paragraph).

**Horak** *et al.* treated small (about 3 mm) and larger (about 6.5 mm) subcutaneous SK-OV 3 tumors in a murine model with a single administration of $lead^{-212}$ labeled HER2/neu monoclonal antibody. The dosage of $lead^{-212}$ was either 10 or 20 μCi at a specific activity of 0.6-1.5 mCi/mg for both tumor sizes. In the small tumors inhibition in tumor growth, but no remission was observed; in the

larger tumors no inhibition of tumor growth was observed. **Hartman** *et al.* treated murine lymphoma cells expressing a human *CD25* gene (SP2/Tac) with bismuth$^{-212}$ labeled humanized anti-Tac monoclonal antibody. The mice inoculated with SP2/Tac were treated when the tumor burden was low, i.e., tumors were not visible, with 100, 200 or 300 (lethal) μCi at a specific activity of 5.9-9.3 mCi/mg. Tumor growth in an established SP2/Tac tumor was not curtailed with the same treatment.

Applicants have amended claim 1 to recite a construct comprising a tumor-specific antibody or an antibody fragment and an alpha-emitting isotope. Additionally, claim 1 is amended to recite a solid tumor greater than 1 mm as disclosed in the specification and is amended to recite that the number of times the construct is administered to kill the tumor increases as the size of the tumor increases as discussed *supra*.

Claims 4 and 7 are rejected because, while being enabling for killing tumors having a diameter of 3-5 mm with a construct having a specific activity of 30 mCi/mg at a dosage of 150-200 μCi per mouse as disclosed by **Hartman** *et al.* (*Cancer Res*, 54: 4362-70

(1994)), the specification does not enable any person skilled in the art to use the invention with any specific activity within the range of 0.05 mCi/mg to 100 mCi/mg and any dosage within the range of 0.1 $mg/m^2$ to 50 $mg/m^2$. **Hartman** *et al.* is as discussed *supra*.

Applicants' invention is drawn to the use of an alpha-emitting radionuclide/antibody conjugate where the radionuclide has a high specific activity designed to deliver at least one alpha track per targeted tumor cell. The specific activity selected is dependent on the isotope and its half-life, the number of binding sites for the antibody on the target cell, the stability of the conjugate at the site upon targeting, the affinity of the conjugate for the target the length of time required to deliver the conjugate and the total number of target sites or nonspecific binding sites in the patient. This is information accessible or within the skill of one in the art to determine without undue experimentation. Knowing this, information mathematical modeling is used to determine a specific activity for the radionuclide (pg. 11, lines 1-24).

.Therefore, what is a high specific activity for one isotope (or even what specific activity is required) varies according to the isotope. A specific activity for $bismuth^{-212}$ of 0.2 mCi/mg is not

sufficiently high to cause specific cell kill for HL 60 cells. The range for bismuth$^{-212}$ and bismuth$^{-213}$ can be about 8 mCi/mg to about 50 mCi/mg depending on the cell type and the other factors, e.g., the number of tumor cells and the number of sites per tumor cell, discussed immediately *supra*. However, actinium$^{-225}$, for example, is significantly more potent than either of bismuth$^{-212}$ or bismuth$^{-213}$. A specific activity of 0.12 mCi/mg for actinium$^{-225}$ demonstrated specific potent cell kill (pg. 43, lines 22-29 and pg. 44, lines 1-7). Applicants have amended claim 4 to recite a range from about 0.1 mCi/mg to about 50 mCi/mg. As discussed *supra*, it would be within the skill of an artisan in this art to determine an appropriate specific activity for a selected radionuclide without undue experimentation. As claim 4 has been amended, the rejection of claim 4 as not being enabling for a specific activity of 100 mCi/mg for bismuth$^{-213}$ is rendered moot.

Furthermore, Applicants submit that dosage is subjective and determination of such is routine in the art. Applicants would like to draw the Examiner's attention to the Examiner's statement in this Office Action that, as per claim 7, "to determine optimum dosage is within the level of ordinary skill in the art" (page 11, lines 13-14).

In the instant application dosage is also dependent on the specific activity of the radionuclide and tumor to be treated. A dosage regimen also is selected based on the size of the recipient, the ability of the recipient to tolerate a particular dosage and the tumor burden. One of ordinary skill in the art would recognize that dosage of a radionuclide has a lethal limit. As such, one would reasonably expect that such an artisan would not be motivated to try administering the maximum specific activity and dosage, i.e. 50000 μCi, as disclosed in the instant invention to a mouse as disclosed in the **Adams** *et al.* reference, without first determining via standard methods that such a treatment protocol would be optimal for the situation.

Claims 1-7 stand rejected as not being enabling for killing a tumor with a diameter greater than 5 mm. This corresponds to a volume of 65.4 $mm^3$ using the Examiner's formula $(d^3 \times 3.14)/6$. **Horak** *et al.* and **Hartman** *et al.* were discussed supra.

Applicants invention was discussed *supra*. Additionally, it is critical in the method of the instant invention that the alpha-emitting construct be administered multiple times, if necessary, to

kill the tumor. The alpha emittor constructs emit high energy linear transfer particles that have a short track length and, as demonstrated in the instant invention for bismuth, an effective range usually not more than 5 or 6 layers of cells. Also, constructs incorporating bismuth$^{-212}$ and bismuth$^{-213}$ have short half lives, i.e., 60 min and 46 min, respectively. Thus, to maximize specific cell killing, the construct must be administered more than once if the diameter of the tumor warrants multiple administrations. As described in the specification, this is like peeling an onion. The construct is administered and about 5-6 layers of tumor cells are killed; the process is repeated and another several layers of cells are killed. This can be done as many times as required depending on the type of tumor and its size. Figure 2 of Applicants' specification demonstrates this effect.

In contrast to **Horak** *et al.*, Applicants claim 1 specifically recites an antibody or antibody fragment and an alpha emitting isotope as comprising the construct and, thus, does not recite lead-212. That **Horak** *et al.* could successfully treat tumors with a diameter of about 3 mm with a single administration of lead$^{-212}$ is because lead$^{-212}$ is initially a beta-emittor with bismuth$^{-212}$ as the

daughter. Beta particles travel faster than alpha particles. Beta emission is over a larger field, i.e., the range is greater, and is not as dependent on specific activity as the instant isotopes. Additionally, lead$^{-212}$ has a half-life that is ten times that of bismuth$^{212}$. Thus, with a single administration of lead$^{-212}$, the beta particles can travel greater distances from the target site. However, with single administration of the isotope, this effect is eventually limited by tumor size. Applicants also reiterate that lead$^{-212}$ did not effect remission in any of the tumors treated.

**Hartman** *et al.* did not administer multiple doses of their bismuth$^{-212}$ radiolabeled constructs so the diameter of the tumors could only be 1 mm or less. The path length of the alpha particle and the specific activity of the bismuth$^{-212}$ used in **Hartman** *et al.* are simply not enough to kill tumors of greater diameters with a single administration of the isotope. As demonstrated with the instant invention, such limits are successfully overcome with a multiple dosing regimen correlating to tumor diameter. The size of the tumor is only limited by the particular tumor to be treated. In light of the claim amendments and arguments presented supra, Applicants

respectfully request that the rejection of claims 1-7 under 35 U.S.C. §112, first paragraph be withdrawn.

The 35 U.S.C. §102(a) rejection

Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by **Horak** *et al.* Applicants respectfully traverse this rejection.

The Examiner states that **Horak** *et al.* teach that tumors having a volume of 15 cubic millimeters could be treated with antibodies labeled with lead$^{-212}$, having a specific activity of 0.6 to 1.5 μCi/μg (p. 1946, first column, and p.1948, second column, second paragraph). Since 0.6 to 1.5 μCi/μg is the same as 0.6 to 1.5 mCi/mg, the specific activity of the labeled antibody as taught by **Horak** *et al.* is within the range of the claimed specific activity as is the volume of the tumor 15 cubic millimeters which corresponds to a tumor with approximate diameter of 3 mm. **Horak** *et al.* was discussed *supra*.

Applicants invention was discussed *supra*. Applicants have amended claim 1 as discussed. As previously discussed, lead$^{-212}$ itself is a beta-emittor; the daughter bismuth$^{-212}$ is the alpha-

emitting nuclide. Also, no teaching is given in **Horak** *et al.* that the bismuth-212 daughter even tracks into the tumor cells. Furthermore, **Horak** *et al.* only hypothesizes that alpha-emitting constructs can be directly used. Applicants' invention specifically designs alpha-emitting constructs to deliver at least one alpha track per tumor cell, thereby effecting tumor kill with a requisite number of administrations. Claim 2is canceled and claim 4 further limits the invention to specific activities of the isotopes and is not anticipated by **Horak** *et al.* if amended claim 1 is not anticipated.

For a valid §102 rejection, the prior art references must contain each element of the claimed invention. Absent teachings of administration of direct and initial administration of an alpha-emitting labeled antibody or that diameter of the tumor determines the number of administrations necessary to kill the tumor, **Horak.** *et al.* does not anticipate Applicants' claimed invention. Therefore, as this reference is not valid prior art against the instant application under 35 U.S.C. §102 and in view of the preceding remarks, Applicants respectfully submit that the cited reference does not anticipate claims 1-4 under 35 U.S.C. §102. Accordingly, Applicants

respectfully request that the rejection of claims 1-4 under 35 U.S.C. §102(a) be withdrawn.

The 35 U.S.C. §103 (a) rejection

Claims 1-7 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Horak** *et al.*, in view of **Hartman** *et al.*, **Kasperson** *et al.* (*Nuclear Med Comm*, 16, pp. 468-476 (1995)) and **Lemelson** (U.S. Patent No. 4,665,897). Applicants respectfully traverse this rejection.

**Horak** *et al.* and **Hartman** *et al.* are discussed *supra*. The Examiner states that **Kasperson** *et al.* teach that $Bi^{-213}$ can be an alternative to $Bi^{-212}$, with the advantage of safer and easier production (p. 475, first col., first paragraph). Further, the Examiner states that **Lemelson** teaches a method of treating tumors comprising administering antibodies containing inactive nuclide that could be rendered radioactive with externally generated radiation, wherein the steps of said method are repeated as many times as necessary to effect remission or destruction of tumors (Claims 28, 35, 36). The particles emitted upon activation include alpha particles.

Thus it would have prima facie obvious to a person of ordinary skill in the art at the time the invention was made to treat tumors of at least 1 mm in size using the method of **Horak** *et al.* or **Hartman** *et al.* by administering an antibody labeled with lead$^{-212}$ or bismuth$^{-212}$ or to substitute them with bismuth$^{-213}$ as taught by **Kasperson** *et al.* It would have been obvious to administer the labeled antibody repeatedly as taught by **Lemelson** to ensure destruction of the tumors. In considering dosage as recited in claims 5 and 7, the Examiner states that determining optimum dosage is within the level of ordinary skill in the art.

**Horak** *et al.* and **Hartman** *et al.* are discussed supra. Additionally, **Horak** *et al.* (Abstract, conclusion); and **Hartman** et al. (Abstract, last paragraph; pg. 4369, col. 2, first complete paragraph) disclose that $Pb^{-212}$ and $Bi^{-212}$, respectively, may be useful in adjuvant, leukemia and intracavity therapy, but it is of limited value in the therapy of established solid tumors due to their respective short half-lives and time to reach the target site. Furthermore, **Hartman** *et al.* demonstrated that bismuth$^{-212}$ delayed or prevented tumor appearance, not that it specifically killed small established solid tumors. The bismuth$^{-212}$/antibody was administered prior to the

occurrence of visible tumors (pg. 4364, last paragraph; pg. 4366-4367, first col.). Applicants submit that if both **Horak** *et al.* and Applicants can show therapeutic effects against solid tumors with a measurable diameter of 1 mm and 3-5 mm, respectively, then the tumors in **Hartman** *et al.* are not small solid tumors.

**Kasperson** *et al.* examined the cytotoxicity of $Bi^{-213}$ *in vitro* and $Ac^{-225}$ immunoconjugates against the human carcinoma cell lines A431 and SW 1398. The reference discloses that $Bi^{-213}$ may be substituted for $Bi^{-212}$ for the treatment of single cell malignancies (pg. 475, col. 1, line 3). Furthermore, the cytotoxic effects of $Bi^{-213}$ in multicell spheroids, considered a more realistic *in vivo* model, were studied. No specific cell-killing was observed using up to 1.2 μCi $Bi^{-213}$ on spheroids with diameters of 0.4 mm to 0.7 mm. **Kasperson** *et al.* state that $Bi^{-213}$ may have limited applicability in the treatment of solid tumors (pg. 474, last paragraph).

**Lemelson** teaches methods of detecting, monitoring and treating a tumor by administering a drug unit comprising a monoclonal antibody and a normally nonradioactive nuclide. The nonradioactive nuclide is activated by external radiation such as neutron radiation. Additionally, the drug unit can comprise another

nuclide, either inactive or low level radioactive. The drug is administered to the patient and activated such that the radiation emitted provides a location and extent of the tumor. Analysis of the signals derived from detectors of the emitted radiation provide a location and direct or reconstructed images of the tumor site provide information on the extent of the tumor. Drug is administered again, activated and the monitoring process repeated until treatment ceases (Abstract; col. 12, lines 1-69; col. 13, lines 1-28).

Both **Hartman** *et al.* and **Kasperson** *et al.* teach away from the instant invention in that these references state that bismuth$^{-212}$ and bismuth$^{-213}$ have limited applicability in treating solid tumors. Thus, one of ordinary skill in the art would not be motivated to use these isotopes as in **Horak** *et al.* Furthermore, it is specific in **Lemelson** that the nuclide used is inactive because the nuclide is used as a means of detecting a tumor and of monitoring the treatment. It is therefore important that the emission of active particles from the nuclide is both controllable and controlled in order to get an accurate image of the tumor. Additionally, no suggestion is found in **Lemelson** that a normally radioactive alpha-emitting isotope can be used even in view of the teaching that any normally

inactive nuclide that subsequently emits an alpha particle upon activation can be used. The instant normally active radionuclides and normally inactive nuclides of **Lemelson** are significantly different elements with significantly differing properties. Absent this suggestion, Applicants submit that one can not make the leap to repeated administrations of bismuth$^{-212}$ or bismuth$^{-213}$ in the method of **Horak** *et al.*, particularly considering **Hartman** *et al.* and **Kasperson** *et al.* teach away from the use of these isotopes for treatment of solid tumors.

In view of the above remarks, Applicants respectfully submit that obviousness can not be established by combining the teachings of the prior art absent some teaching, suggestion or motivation supporting the combination to do so. Absent motivation in **Hartman** *et al.* and **Kasperson** *et al.* to use bismuth$^{-212}$ or bismuth$^{-213}$ to treat established solid tumors and further absent a suggestion or teaching in **Lemelson** of using a normally radioactive alpha emitting nuclide in the disclosed method, Applicants' invention as recited in amended claim 1 is not rendered obvious by combining any of **Hartman** *et al.*, **Kasperson** *et al.*, or **Lemelson** with **Horak** *et al.* Thus, the invention as a whole was not obvious to one of

ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1-7 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed May 8, 2002. If any issues remain, the Examiner is respectfully requested to telephone the undersigned attorney for immediate resolution. Applicants believe that no fees are due, however, should this be in error, please debit Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

Respectfully submitted,

Date: August 15, 2002

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

## IN THE CLAIMS:

Please amend claim 1 as follows:

1. A method of killing a solid tumor greater than 1 mm in size in an individual in need of such treatment, comprising the step of:

administering ~~to said individual~~ a pharmacologically effective dose of a construct at least once to said individual, said construct comprising an antibody or an antibody fragment specific to said tumor and an alpha emitting isotope; wherein the number of administrations of said construct necessary to kill said tumor increases as the size of said tumor increases.

Please amend claim 3 as follows:

3. The method of claim 1, wherein said alpha emitting isotope is ~~selected from the group consisting of B~~ bismuth-213, ~~B~~ bismuth-212, ~~a n~~ actinium-225, radium-223, ~~lead-212~~, turbium-149, fermium-~~1~~ 255 ~~and~~ or astatine-211.

Please amend claim 4 as follows:

4. (amended) The method of claim 3, wherein said alpha emitting isotope has a specific activity of from about ~~0.05~~ 0.1 mCi/mg to about ~~100~~ 50 mCi/mg.

Please cancel claims 2 and 6.